Influence of Preoperative Radiation Field on Postoperative Leak Rates in Esophageal Cancer Patients after Trimodality Therapy

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Introduction: Postoperative morbidities, such as anastomotic leaks, are common after trimodality therapy (chemoradiation followed by surgery) for esophageal cancer. We investigated for factors associated with an increased incidence of anastomotic leaks.

Methods: Data from 285 esophageal cancer patients treated from 2000 to 2011 with trimodality therapy were analyzed. Anastomotic location relative to preoperative radiation field was assessed using postoperative computed tomographic imaging. Logistic regression was used to evaluate for factors associated with any or clinically relevant (CR) (≥ grade 2) leaks.

Results: Overall anastomotic leak rate was 11% (31 of 285), and CR leak rate was 6% (17 of 285). Multivariable analysis identified body mass index (odds ratio [OR], 1.09; 95% confidence interval [CI], 1.00–1.17; OR, 1.11, 95% CI, 1.01–1.22), three-field surgery (OR, 10.01; 95% CI, 3.83–26.21; OR, 4.83; 95% CI, 1.39–16.71), and within radiation field ("in-field") anastomosis (OR, 5.37; 95% CI, 2.21–13.04; OR, 8.63; 95% CI, 2.90–25.65) as independent predictors of both all grade and CR leaks, respectively. While patients with distal esophageal tumors and Ivor-Lewis surgery had the lowest incidence of all grade (6.5%) and CR leaks (4.2%), most of the leaks were associated with the anastomosis constructed within the field of radiation (in-field: 39% and 30% versus out-of-field: 2.6% and 1.0%, respectively, for total and CR leaks, p less than 0.0001, Fisher's exact test).

Conclusions: Esophagogastric anastomosis placed within the preoperative radiation field was a very strong predictor for anastomotic leaks in esophageal cancer patients treated with trimodality therapy, among other factors. Surgical planning should include a critical evaluation of the preoperative radiation fields to ensure proper anastomotic placement after chemoradiation therapy.

Key Words: Anastomotic leaks, Esophagectomy, Radiation, Esophageal cancer, Trimodality therapy.

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Surgical resection alone remains a worldwide standard for the management of esophageal cancer, but the 5-year survival usually does not exceed 20%.[1] Neoadjuvant chemoradiation before surgical resection (trimodality therapy) allows for disease downstaging and increases tumor resectability, with increased cure rates. Older randomized trials demonstrated probable survival benefit of preoperative chemoradiation although a number of negative studies made the indication controversial. A meta-analysis of the trials showed a 2-year overall survival benefit of 13% for patients treated with neoadjuvant chemoradiation followed by surgery compared with patients treated with surgery alone.[2] Recently, a large randomized trial demonstrated significant improvement in overall survival and disease-free survival with the use of neoadjuvant chemoradiation compared with surgery alone.[3] Chemoradiation before surgery improved median overall survival to 49.4 months compared with 24.0 months in patients treated with surgery alone.

However, preoperative chemoradiation increases the chance for toxicity and postoperative morbidity compared with surgery alone. There are several nonrandomized studies in the literature that showed an increase in surgical morbidity in patients undergoing neoadjuvant chemoradiation.[4–7] Postoperative pulmonary complications have been well studied and have been shown to be related to radiation dose to the lungs.[8]

The effects of neoadjuvant radiation on postoperative anastomotic leaks have been less extensively studied. In an older study, anastomotic leaks were found in 17% of patients who underwent esophagectomy with cervical anastomosis; however, the use of preoperative radiotherapy was not associated with the incidence of leaks.[9] A systematic review showed that reports in the literature for anastomotic leak rates vary between 0% and 26% and that the leak rate is not influenced by method of anastomosis, either stapled or hand-sewn.[10] A recent Belgian study with 54 patients treated with neoadjuvant

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radiation followed by Ivor-Lewis esophagectomy showed that the dose to the gastric fundus was a significant predictor for anastomotic complications (leakage, ischemia, and stenosis).[11]

The aim of the present study was to determine the clinical and dosimetric factors that can influence the risk of developing any grade leaks or the more clinically relevant leaks of ≥ grade 2 (or what we will term as "CR leaks" throughout the article) in patients undergoing trimodality therapy. Dose to the whole stomach and associated gastric substructures were studied as well as the impact of the positioning of radiation field and the location of the anastomotic site.

PATIENTS AND METHODS

Patient Data

This investigation was approved by the institutional review board and was conducted in compliance with the Health Insurance Portability and Accountability Act. This was a retrospective analysis of esophageal cancer patients treated at M. D. Anderson Cancer Center with neoadjuvant chemoradiation followed by surgery between 2000 and 2011. Because we wanted to evaluate the radiation dosimetry to the stomach, only patients with full dose-volume histogram data were included. Patients who had gastrectomy were excluded. We also included only patients treated with photon-based therapy (three-dimensional conformal radiation therapy [3D-CRT] or intensity-modulated radiation therapy [IMRT]).

A thorough chart review was done to document the clinical and treatment-related factors for this cohort of patients. Following surgery, follow-up monitoring included interval history and physical examination at the discretion of the treating physicians. Incidence of perioperative anastomotic leaks was recorded by grade for each patient, defined as radiographic leak only (grade 1), minimal intervention/stent placement (grade 2), major intervention/reoperation (grade 3), and conduit loss (grade 4). CR leaks were defined as leaks ≥ grade 2. Postsurgical computed tomography (CT) scans were examined to determine if surgical anastomosis was in or out of the radiation field. Contouring of the whole stomach, fundus, antrum, and lateral body was done by one person using the Pinnacle planning software. Associated 3D and IMRT treatment plans were used to generate dose-volume histograms for each of the contoured gastric regions of interest.

Treatment Approach

Patients in this study cohort were treated with neoadjuvant chemoradiation of 50.4 Gy at 1.8 Gy per fraction. Combinations of 5-fluorouracil and taxane, or with platinum-based compounds were administered concurrently with radiotherapy. Several weeks after completion of chemoradiation, most patients were restaged using CT, positron emission tomography/CT, or esophagoduodenoscopy (EGD) with biopsy of the primary disease site and evaluated for surgical management. The most common esophagectomy procedure was Ivor-Lewis, whereas a few patients also received transhiatal, left thoracotomy, radical (en block) resection, or minimally invasive esophagectomy.

The technique of 3D-CRT or IMRT was used for this patient cohort. The internal gross tumor volume was delineated based on the four-dimensional CT simulation images to account for tumor motion relative to diaphragmatic motion, fluorodeoxyglucose (FDG)-positron emission tomography/CT, and endoscopy results. The clinical target volume (CTV) included the internal gross tumor volume with a radial margin of 0.5 to 1 cm and a proximal and distal margin of 3 to 4 cm. Elective nodal regions were not covered, unless in the proximal locations where the supraclavicular fossa bilaterally were included in the target volume, and in the distal esophagus where the celiac axis was covered if it was involved. The nodal CTV was defined by 0.5 to 1 cm expansion from the nodal gross tumor volume. The planning target volume was the CTV plus a uniform 0.5-cm expansion margin.

Statistical Methods

Logistic modeling was used to assess associations between leak incidence and various continuous and categorical variables. The continuous variables studied were age, body mass index (BMI), tumor length, planning target volume, prescribed dose, and mean dose to whole stomach, lateral body, antrum, and fundus. Categorical variables studied were Karnofsky Performance Status, coronary artery disease history, diabetes history, smoking history, tumor location, presence of in-field anastomosis, radiation modality, use of induction chemotherapy, salvage surgery (defined as ≥90 days after chemoradiation), surgical margin status (R0 versus R1–2), and type of surgery (Ivor-Lewis, transhiatal, three-field, or hybrid). Logistic regression analysis was then used to perform multivariable analysis of factors that were significant ($p \leq 0.05$) on univariable analysis. The two-tailed Fisher's exact test was used to test the significance of proportions.

RESULTS

Patient Cohort

A total of 285 patients diagnosed with esophageal cancer and treated with neoadjuvant chemoradiation followed by esophagectomy were included in our analysis; 158 patients were treated with 3D-CRT and 127 were treated with IMRT. Concurrent chemotherapy was given to all patients during chemoradiation, and 151 patients were treated with induction chemotherapy before chemoradiation. Following radiation, the most common surgical procedure was Ivor-Lewis surgery (n = 222) followed by three-field and transhiatal surgery (n = 31 and 29, respectively). Three patients had hybrid open thoracotomy/laparoscopy resections. Nearly all of the patients had creation of a gastric conduit (97.9%, 279 of 285) with only five cases of jejunal interposition (for one case the origin of the conduit is not known). There was no association between leaks and jejunal interposition (3 of 5 had no leaks).

Factors Associated with Anastomotic Leaks

Overall, there were 14 grade 1, 8 grade 2, 8 grade 3, and 1 grade 4 leaks. Anastomotic leaks of any grade occurred in 31 patients for an overall incidence rate of 11%, and 17 patients (6%) had grade 2 or higher leaks. Table 1 shows patient and treatment-related characteristics that were associated with the

TABLE 1. Univariable Analysis of Factors Associated with Anastomotic Leaks

			All Grades		Grade ≥ 2	
Continuous Variables	**Median**	**Range**	**OR**	***p***	**OR**	***p***
Age (yr)	61	29–79	0.99	0.590	1.01	0.818
BMI (kg/m^2)	28	5.3–50.3	1.05	0.136	**1.10**	**0.031**
Tumor length (cm)	5	0–15	0.95	0.537	0.98	0.888
PTV (cm^3)	759	127–2609	1.00	0.733	1.00	0.547
Mean dose stomach (Gy)	39.1	0.04–60.4	**0.97**	**0.035**	0.99	0.478
Mean dose lateral body (Gy)	44.4	0.05–68.6	**0.98**	**0.028**	0.98	0.166
Mean dose fundus (Gy)	48.3	0.06–70.0	**0.97**	**0.025**	0.98	0.245
Mean dose antrum (Gy)	21.9	0.02–55.2	0.98	0.176	1.01	0.668
			All Grades		**Grade ≥ 2**	
Categorical Variables	**Reference (N)**	**Comparator (N)**	**OR**	*p*	**OR**	*p*
KPS	70–80 (133)	90–100 (145)	1.24	0.576	0.59	0.305
Diabetes	Yes (42)	No (243)	2.25	0.071	**3.52**	**0.020**
Alcohol use	Yes (61)	No (223)	1.31	0.535	2.10	0.161
Coronary artery disease	Yes (24)	No (260)	1.73	0.350	1.48	0.615
Smoking history[a]	Yes (198)	No (85)	0.76	0.484	1.42	0.548
Tumor location	Upper-mid (21)	Lower (163)	**4.98**	**0.002**	**4.52**	**0.016**
In-field anastomosis	Yes (44)	No (241)	**6.15**	**<0.001**	**9.83**	**<0.001**
Induction chemotherapy	Yes (151)	No (134)	0.81	0.588	0.77	0.615
Radiation modality	IMRT (127)	3D (158)	0.89	0.755	1.11	0.831
Type of surgery	Three-field (31)	Others (254)	**9.47**	**<0.001**	**5.30**	**0.002**
Salvage surgery	Yes (40)	No (245)	0.90	0.848	0.81	0.781
Margin status	R1–2 (39)	R0 (246)	2.02	0.133	1.14	0.625

[a]N = 35 were unknown and excluded.
BMI, body mass index; IMRT, intensity-modulated radiation therapy; KPS, Karnofsky Performance Status; OR, odds ratio; PTV, planning tumor volume.
Bold indicates p values < 0.05

occurrence of any or CR anastomotic leak based on univariable analysis. For any grade leaks, tumor location, in-field anastomosis, and type of surgery (three-field versus others) were factors associated with anastomotic leaks. In addition, lower mean doses to stomach and substructures were associated with increased incidence of anastomotic leaks. For CR leaks, BMI, diabetes, tumor location, in-field anastomosis, and the type of surgery were significant factors associated with the occurrence of leaks.

Multivariable Analysis

Stepwise forward and backward multivariable analyses were performed using candidate factors that were significant at p less than 0.05 on univariable analysis. Subsequently, factors that were not included as candidate factors in the initial multivariable analysis because of the lack of univariable significance were tested for their ability to improve the model fit. For both all grade and CR leaks, the factors selected as independent predictors were BMI, three-field surgery, and in-field anastomosis (Table 2).

Incidence of Leaks Associated with the Predictive Factors

Patients with anastomosis done inside the radiation field had a significantly higher incidence of leaks of all grades when compared with anastomoses that were placed outside the radiation field (31.8% versus 7%, $p < 0.0001$). Findings were similar for high-grade leaks as well (15.9% versus 3.7%, $p < 0.0001$). We evaluated the incidence of CR anastomotic leaks in relation to the significant factors that were discovered in the multivariable analysis. For BMI, we analyzed the incidence of CR leaks using the median BMI (28 kg/m^2) as a cutoff. The incidence of any grade leaks only trended for but was not significantly lower in patients with a BMI less than 28 kg/m^2 (12 of 143, 8.4%) than in patients with BMI greater than or equal to 28 kg/m^2 (19 of 142, 13.4%, $p = 0.189$). However, the incidence of CR leaks was statistically significantly lower in patients with a BMI less than 28 kg/m^2 (4 of 143, 2.8%) than in patients with BMI greater than or equal to 28 kg/m^2 (13 of 142, 9.2%, $p = 0.025$).

While upper/middle tumor location was a significant risk factor for the development of anastomotic leak on univariable analysis, this factor was no longer significant on multivariable analysis. The reason is that tumor location was strongly associated with the probability of in-field anastomosis: 14 of 21 patients with upper/middle tumors had in-field anastomosis (67%) compared with 30 of 263 patients with lower tumors (11%) ($p < 0.001$). To take this further, we evaluated the incidence of CR leaks based on tumor location and anastomotic location relative to the radiation field (Table 3). The large majority (92%) of patients in our

TABLE 2. Multivariable Analysis of Significant Predictors of Anastomotic Leaks

	All Grades			Grade ≥ 2		
Variables	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
BMI	1.09	1.00–1.17	0.032	1.11	1.01–1.22	0.021
Three-field surgery	10.01	3.83–26.21	0.000	4.83	1.39–16.71	0.013
In-field anastomosis	5.37	2.21–13.04	0.000	8.63	2.90–25.65	0.000

BMI, body mass index; CI, confidence interval; OR, odds ratio.

TABLE 3. Anastomotic Leaks in Relation to Anastomosis Location

		In-Field (N = 14)		Out-of-Field (N = 7)		
Tumor Location (N)	**Total Leaks (%)**	**N**	**%**	**N**	**%**	***p***
Upper/middle (21)	7 (33)	5	35.7	2	28.6	1.000
		In-Field (N = 30)		**Out-of-Field (N = 233)**		
Tumor Location (N)	**Total Leaks (%)**	**N**	**%**	**N**	**%**	***p***
Distal (263)	24 (9)	9	30	15	6.4	0.0004
	$p = 0.0036$		$p = 0.7384$		$p = 0.0804$	
		In-Field (N = 14)		**Out-of-Field (N = 7)**		
Tumor Location (N)	**Grade ≥ 2 Leaks (%)**	**N**	**%**	**N**	**%**	***p***
Upper/middle (21)	4 (19)	3	21	1	14	1.000
		In-Field (N = 30)		**Out-of-Field (N = 233)**		***p***
Tumor Location (N)	**Grade ≥ 2 Leaks (%)**	**N**	**%**	**N**	**%**	
Distal (263)	13 (5)	7	23	6	2.5	0.0001
	$p = 0.0280$		$p = 1.000$		$p = 0.1893$	

p value significance comparing groups vertically or horizontally.

cohort had tumors located in the lower third of the esophagus. When compared with patients with lower esophageal cancers, the overall leak rate was significantly higher for patients with upper esophageal tumors (33% versus 9%, $p = 0.004$). This was also true for CR leaks (19% versus 5%, $p = 0.028$). However, leaks rates were nearly equal regardless of tumor location if the anastomosis was in-field. For all grades of leaks, patients with both in-field anastomosis and an upper or middle esophagus tumor location had an anastomotic leak rate at 36% (5 of 14), which was not different from the patients with distal tumors and in-field anastomosis (9 of 30, 30%, $p = 1.00$). This was also true for CR leaks (21% versus 23% for upper/middle versus distal location, respectively). For patients with out-of-field anastomosis, the leak rate seems to differ based on tumor location, with higher leak rates for upper/middle location compared with distal locations, but these were not statistically significant (Figure 1). On the contrary, patients with distal esophageal tumors and an out-of-field anastomosis had a total leak rate of 6.4%, which was statistically significant compared with in-field anastomosis of 30% ($p = 0.0004$) (Figure 2). For CR leaks, distal locations had only a 2.5% risk if the anastomosis was out of field, which was significantly lower than the risk of in-field anastomosis (23%, $p = 0.0001$). To remove the potential confounding factor of the different surgery techniques used for tumors in the distal location, we confined our analysis to only the patients who had Ivor-Lewis esophagectomies ($n = 215$). The overall leak rate was 6.5% and the CR leak rate was 4.2%. We found that the rate of all grade and CR leaks were 39% (9 of 23) and 30% (7 of 23), respectively, when the anastomosis was placed in-field versus 2.6% (5 of 192) and 1.0% (2 of 192), respectively, if the anastomosis was placed out-of-field. The differences were highly significant ($p < 0.0001$).

The differences in incidence of all grade and CR leaks were also significantly influenced by the type of surgery. The observed incidence rates for all grades and CR leaks were 16 of 222 (7.2%) and 10 of 222 (4.5%) for Ivor-Lewis, 13 of 31 (41.9%) and 6 of 31 (19.4%) for three-field surgery, 2 of 29 (7%) and 1 of 29 (3.4%) for transhiatal surgery, and 0 of 3 and 0 of 3 for patients who had hybrid surgery, respectively. To determine if three-field surgery was associated with an even higher rate of complications, we examined grade 3 and higher leaks and association with the type of surgery. Only 2 of 31 (6.4%) with three-field surgery had grade 3–4 leaks when compared with 7 of 254 (2.8%) who received other types of surgery, the difference of which was not statistically significant (odds ratio, 2.43; $p = 0.281$).

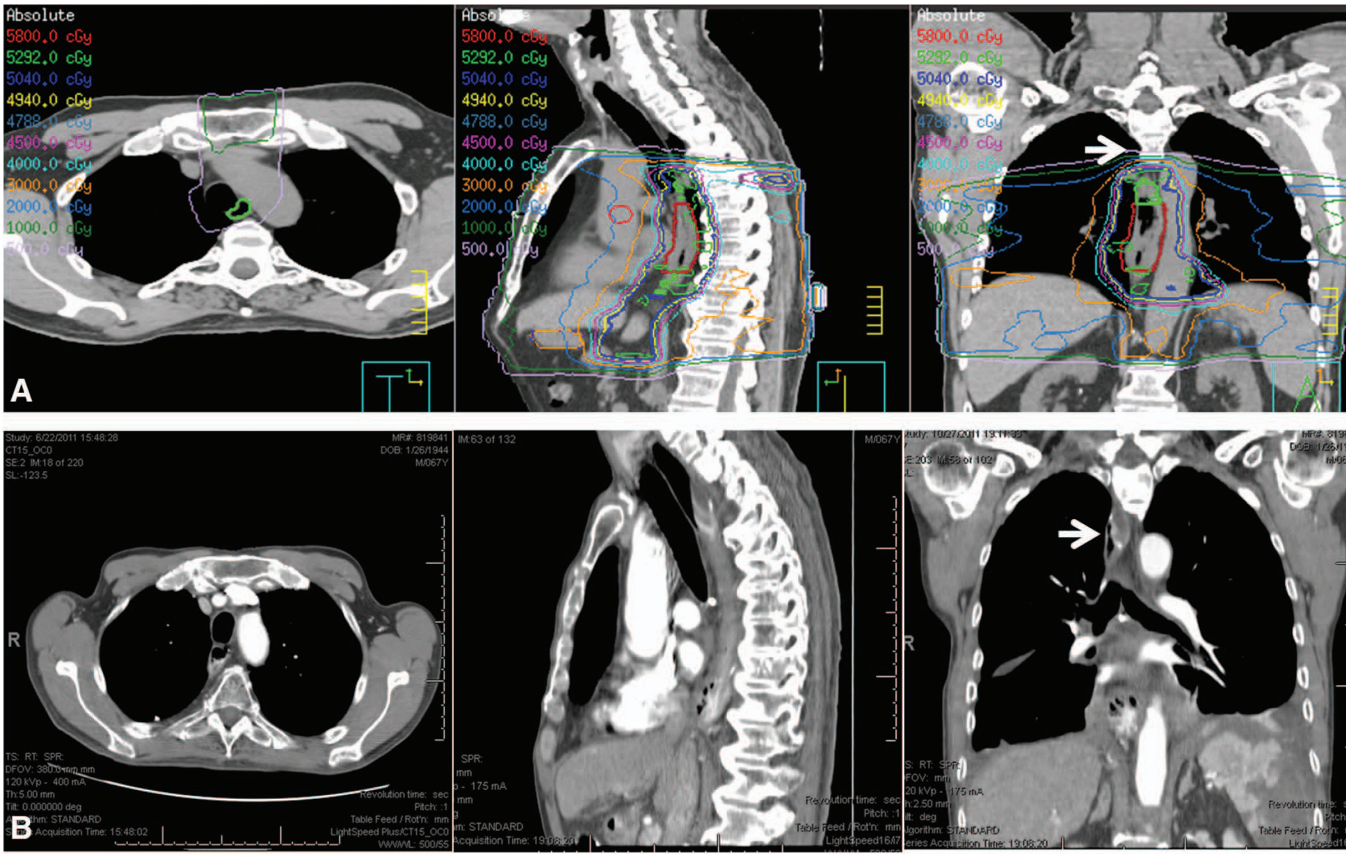

FIGURE 1. Illustration of a case with out-of-field anastomosis. *A*, Simulation CT imaging of a midesophageal tumor with treatment plan encompassing areas below the aortic arch. *B*, Post-Ivor-Lewis esophagectomy CT imaging showing postoperative anatomy. White arrows point to the area of anastomosis above the aortic arch. This patient did not develop anastomotic leak. CT, computed tomography.

DISCUSSION

Our findings in this study demonstrated that the anastomotic location relative to the field of radiation is an important factor influencing the occurrence of postoperative leaks after esophagectomy. Although there are reports to suggest that neoadjuvant therapy, either chemotherapy or radiation, does not substantially increase the postoperative morbidity for patients who undergo esophagectomies,[12] there is substantial evidence in the literature to suggest that neoadjuvant chemoradiation increases the rate of postoperative morbidity and mortality. A meta-analysis of randomized trials of patients with resectable esophageal cancer showed that chemoradiation was a risk factor for postoperative mortality (odds ratio, 1.18–3.73; p = 0.01).[13] A Japanese retrospective analysis of 686 esophageal cancer patients also showed that neoadjuvant chemoradiation was an independent predictor for postoperative complications with an anastomotic leak rate of 28% in patients who received neoadjuvant radiation compared with 16.5% in patients who had surgery alone ($p < 0.05$).[14] Our observed total leak rate of 11% was comparatively lower, but this could be due, in part, to the surgical approaches used in the different studies, since in the published studies the rates were only about 7% for both transhiatal and Ivor-Lewis patients, which is about what we see for our patient cohort who received Ivor-Lewis esophagectomy (6.5%). We found that three-field esophagectomy was a significant risk factor for anastomotic leak on multivariable analysis with a leak rate of 42%.

Vande Walle et al.[11] reported a 5.6% anastomotic leak rate in their study showing the significance of D_{50} to the gastric fundus (the total dose delivered to 50% of the volume) as a risk factor for anastomotic complications. To our knowledge, this was the only published evidence that showed radiation dose to the stomach as a risk factor for anastomotic complications. Although we did find an association of the mean dose to the stomach and substructures to the incidence of all grade leaks, the higher mean dose was associated with a protective effect rather than a detrimental effect. We believe that this paradoxical effect was attributed to the mean dose being inversely related to both the incidence of in-field anastomosis and three-field surgery (Supplementary Figure 2, Supplemental Digital Content, http://links.lww.com/JTO/A536). Patients with upper and middle esophagus tumors were significantly more likely to have anastomotic leaks because more in-field anastomosis occurs in this location and, consequently, have lower dose to the gastric structures. Three-field surgery was also more likely to be in upper-esophageal locations (12 of 21, 57%) compared with the lower esophageal location (19 of 263, 7.2%) ($p < 0.0001$). Although patients with lower

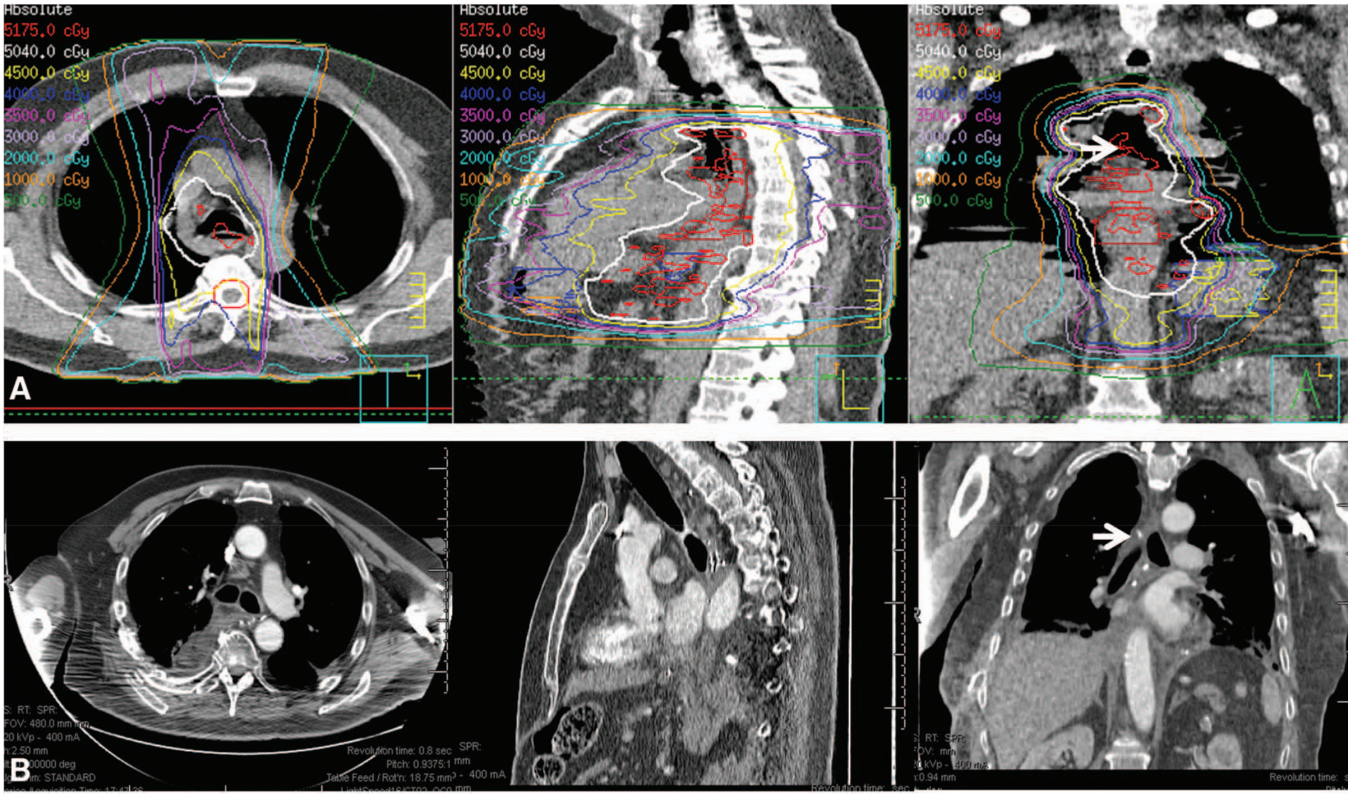

FIGURE 2. Illustration of a case with in-field anastomosis. *A*, Simulation CT imaging of a midesophageal tumor with treatment plan encompassing areas below the aortic arch. *B*, Post-Ivor-Lewis esophagectomy CT imaging showing postoperative anatomy. White arrows point to the area of anastomosis at the level of carina within the radiation treatment field. This patient developed grade 3 anastomotic leak. CT, computed tomography.

esophageal tumors were associated with increased dose to the stomach, this did not increase the rate of anastomotic breakdown. Surgeons at our institution often take special care to exclude the irradiated stomach when creating the esophagogastric anastomosis.

There have been other factors that are associated with anastomotic leaks regardless of the use of neoadjuvant chemoradiation. An earlier study from India found that low albumin, tumor involvement of the anastomotic cut margin, and cervical anastomosis were predisposing factors for leaks in patients who had upfront surgery.[15] A second study, also in primary resected patients for both benign and malignant disease, found active smoking history, postoperative arrhythmias, and manually sewn versus side-to-side stapled anastomosis as risk factors for leaks.[16] Although we were able to identify some patient factors, such as diabetes and higher BMI, as risk factors for anastomotic leaks, most of what we identified as critical risk factors were related to the tumor location, the type of surgery, and where the anastomosis was placed. We believe that the different findings between our study and the aforementioned ones were primarily due to the use of chemoradiation in all the patients included in our study, which likely overshadowed other potential risk factors. A major finding of our study was that esophagogastric anastomosis placed in the previously irradiated field was significantly associated with increased leak rate. For these cases, irradiated normal tissues in proximity to the normal esophagus were included in the proximal portion of the esophagogastric anastomosis. Patients with upper or middle esophageal tumor location have their radiation treatment portals at or near the sites of thoracic or cervical anastomosis and therefore are more likely to have high doses of radiation targeted to normal tissue in this region. Upper/middle tumor location was a significant predictor of anastomotic leak on univariable analysis but was not included in the multivariable model, when the anastomotic site relative to the radiation field was taken into account. The leaks in the distal location were nearly fully accounted for by whether the anastomosis was placed in-field or out-of-field. However, the incidence of leaks in the upper/middle esophageal location was high regardless of whether the anastomosis was done in-field or out-of-field. Perhaps the number of cases was too small in this location to determine a statistically significant relationship with the field of anastomosis, but there could be other anatomic or clinical factors that were not accounted for that place the upper/middle tumor location at higher risk of developing leaks, independent of the type of surgery or the field of anastomosis.

To our knowledge, there was only one previous study that had evaluated the relationship of radiation field with anastomotic leak rates. This was in a cohort of 38 patients treated with radiation and esophagogastrectomy. They found that there was no increased leaks observed when the anastomosis was located in the preoperative radiation field.[17] The reason for the discrepancy between their study and ours is unclear, but it is likely that the number of patients in their study was too small to make a significant association. It is well established that radiation leads to damage to the microvasculature and the resulting ischemia can slow tissue healing in irradiated fields.[18–20] Patients with diabetes often have issues with microvasculature and wound healing as well. Our analysis also showed a higher leak rate for patients with diabetes, though it was not statistically significant on multivariable analysis (19% versus 9.5%, $p = 0.101$, Table 1).

Our study is limited by the retrospective nature of the analysis, which cannot account for all potential factors that could explain some of our findings. While the surgical procedures at our institution have been standardized to a certain extent, multiple surgeons were involved over the time span of the study so some variation inevitably exists. Furthermore, anatomic configuration and blood supply to both the stomach and the esophagus are varied across the patient population, posing a potential confounding factor that could not be accounted for in a retrospective analysis.

In conclusion, the present study demonstrates that the placement of the esophagogastric anastomosis within the preoperative radiation field is a strong, independent predictor for anastomotic leaks in esophageal cancer patients treated with trimodality therapy. These results have important implications in careful preoperative planning to minimize postoperative leak complications.

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